Fraunhofer
IZI

FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

ANNUAL REPORT 2018
SHORT VERSION

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This is the abridged version of the Fraunhofer IZI Annual Report 2018.

The full version can be found at www.izi.fraunhofer.de/en/publications
The report includes a detailed description of selected projects and a list of this year's publications, besides a number of other features.

Scan the QR codes to go straight to the relevant sections of the annual report.
We recommend that you use the Mozilla Firefox browser for an optimal page display.

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HIGHLIGHTS 2018

HIGHLIGHTS 2018

2018 was a very special year for Fraunhofer IZI for a number of reasons – with the change in the institute's management board and the fresh impetus this gives the scientific orientation of the institute, as well as another positive annual balance sheet and various successful project developments throughout the course of the year. By the end of the year, the institute was able to report a total of 638 employees across its five German sites, who turned over a financial volume of 35.2 million euros, wrote over 300 publications and conference papers, and supervised 53 graduations.

January

- The Fraunhofer Cluster of Excellence for Immune-Mediated Diseases (CIMD) was founded. www.cimd.fraunhofer.de

March

- The GLP test facility was recertified and the Halle (Saale) site expanded.

April

- Positive evaluation of the Department of Drug Design and Target Validation (MWT) in Halle (Saale). The future of the off-site department is now secured from January 1, 2019, when it will be included in the regular federal and state financing received by the Fraunhofer-Gesellschaft.

July

- For the first time ever, the institute was authorized to manufacture a therapeutic antibody as an investigational medicinal product in accordance with Section 13 of the German Medicinal Products Act (AMG).

August

- Novartis drug Kymriah® was approved by the European Commission and the collaboration with Fraunhofer IZI was continued.
- A research facility was set up to inactivate pathogens using low-energy electron beams on an industrial scale. Funding was received from the Bill & Melinda Gates Foundation.

September

- The "protein misfolding diseases" junior researcher group was founded in Halle (Saale).
- The Marie Skłodowska-Curie Innovative Training Networks held their kick-off meeting, focusing on CAR NK cells.
- The Fraunhofer Life Science Symposium was held in honor of institute founder Professor Frank Emmrich. www.fs-leipzig.de

October

- Fraunhofer Project Center Microelectronic and Optical Systems for Biomedicine (MEOS) opened its doors in Erfurt.

STRUCTURES AND FIGURES 2018

PORTRAIT OF THE INSTITUTE

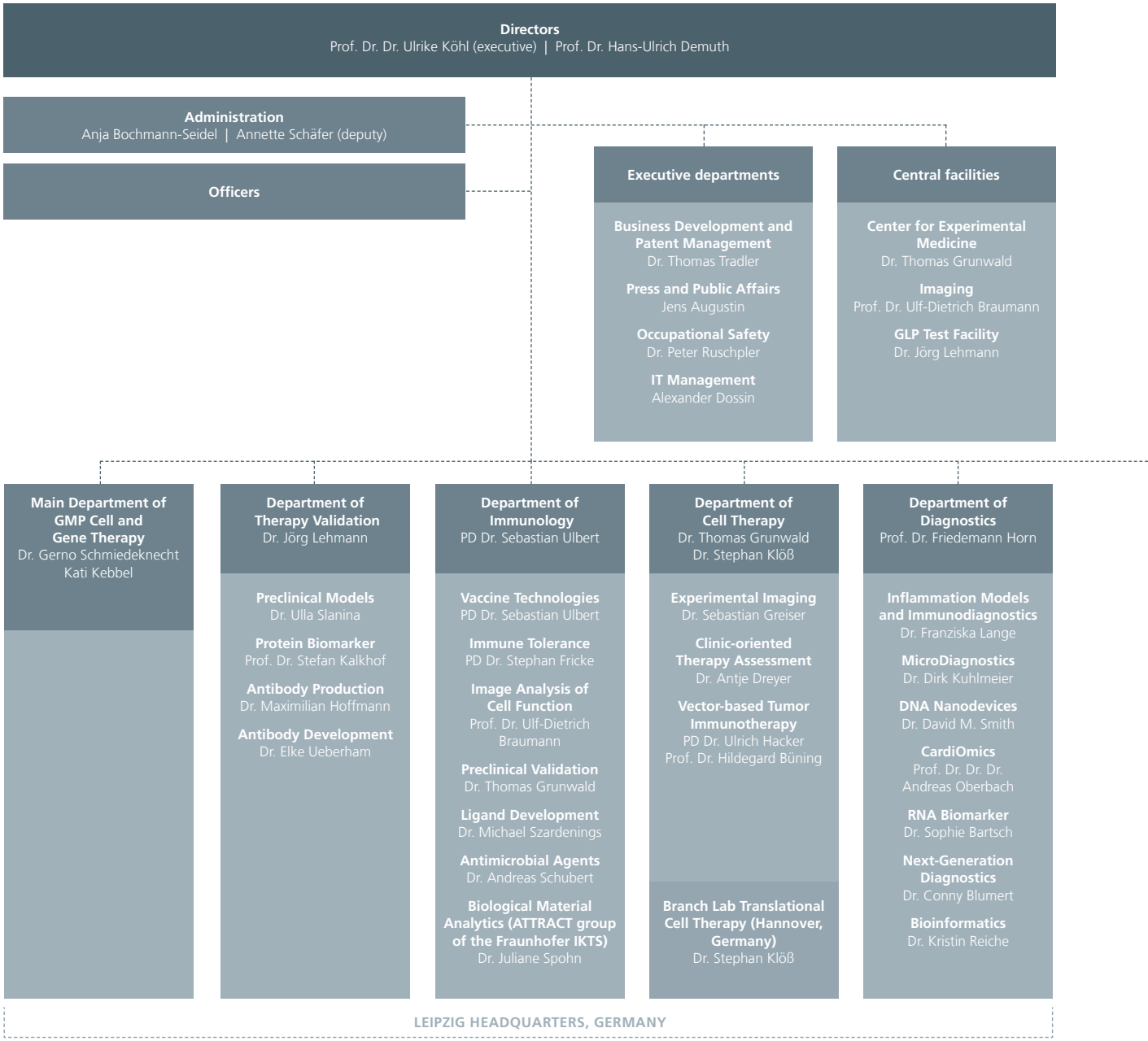
In light of an aging society and an increasing number of chronic diseases, modern medicine is facing exceptional challenges. The Fraunhofer Institute for Cell Therapy and Immunology IZI is working on meeting the demands of health and quality of life through new developments in the fields of diagnostics and therapy. Our body's immune detection and defense system are of particular interest here, as well as cell-biological assay and treatment methods.

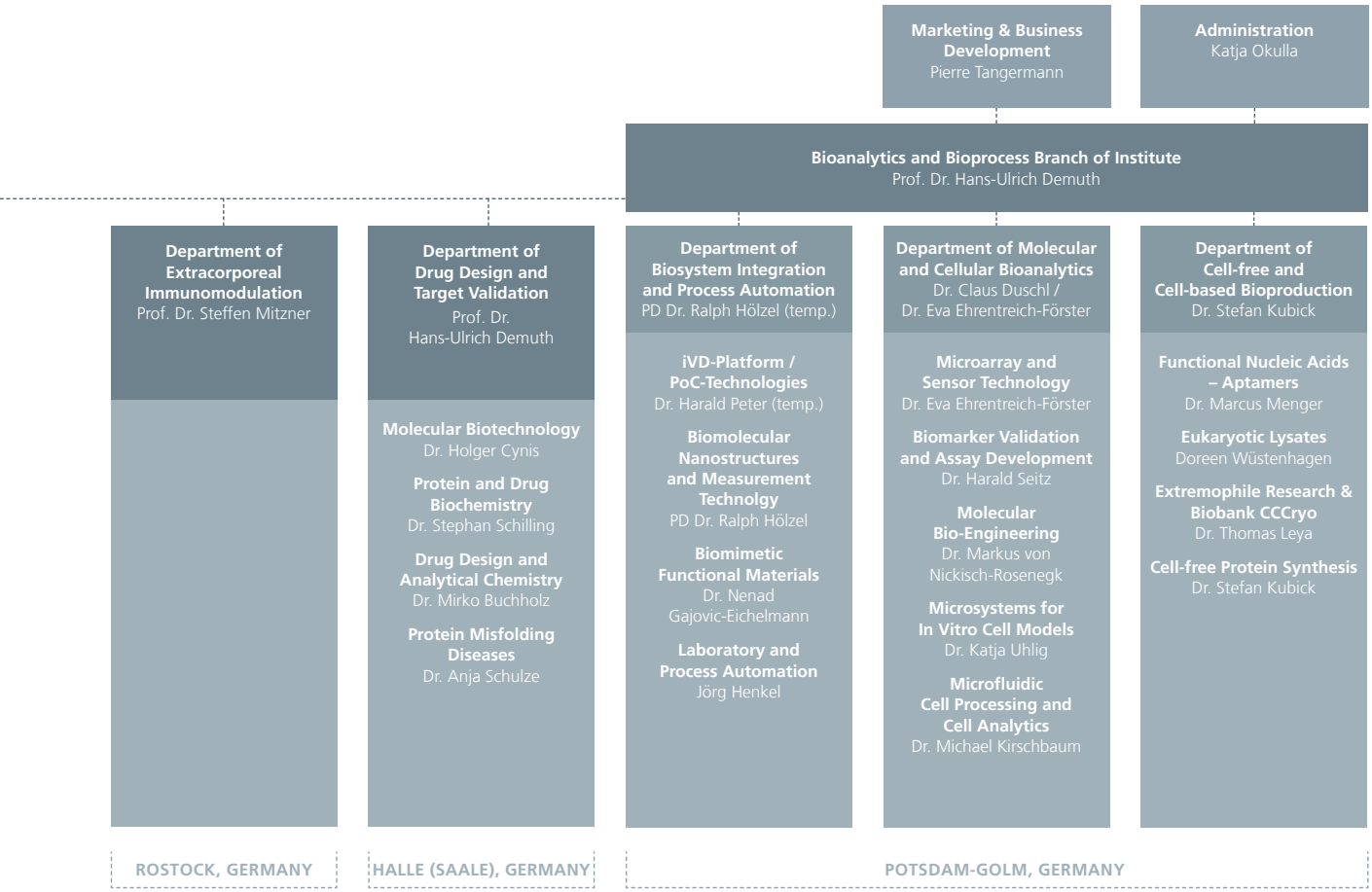
The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute's main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research institutes operating in the field of biotechnology, pharmaceuticals and medical engineering.

The Fraunhofer IZI develops, optimizes and validates methods, materials and products for the business units Cell and Gene Therapy, Drugs and Diagnostics. Its areas of competence lie in cell biology, immunology, drug biochemistry, bioanalytics and bioproduction as well as process development and automation. In these areas, research specifically focusses on the indications oncology, immunological diseases as well as infectious diseases and neurodegenerative diseases.

The institute works in close cooperation with hospital institutions and performs quality tests besides carrying out the GMP-compliant manufacture of clinical test samples. Furthermore, it helps partners obtain manufacturing licenses and permits.

ORGANIZATION*





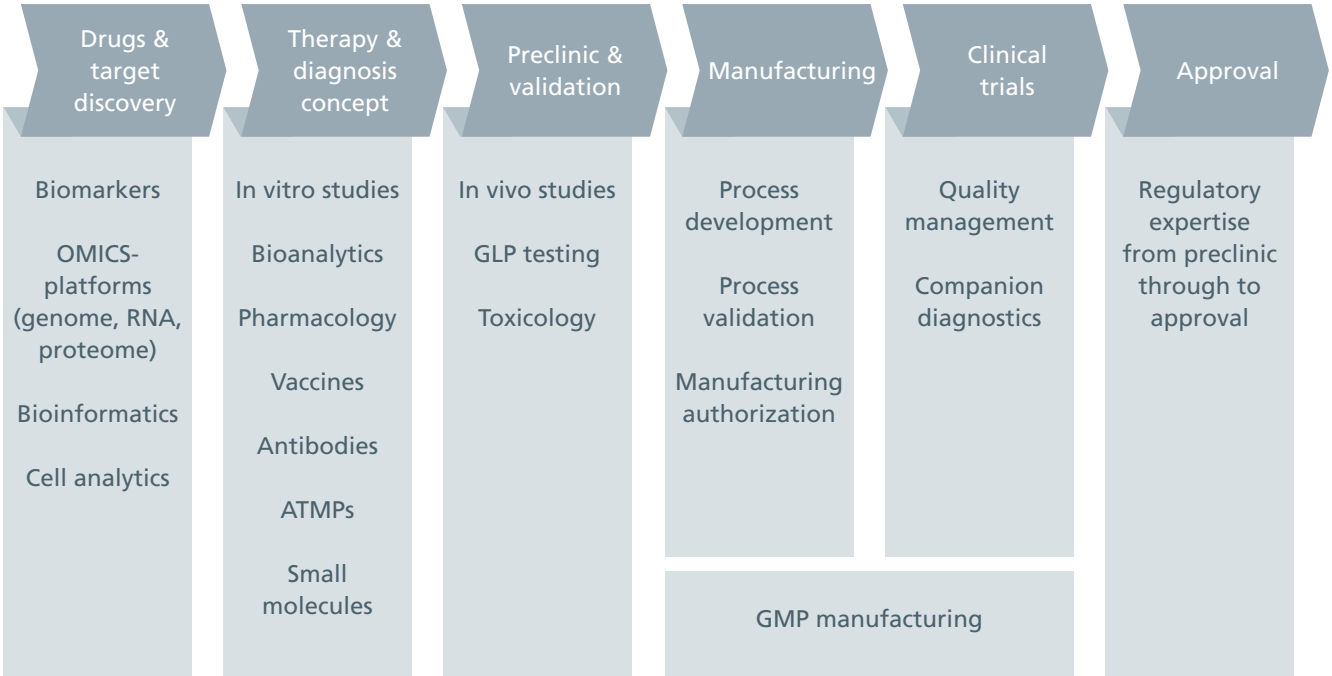
**January 2019*

BUSINESS UNITS

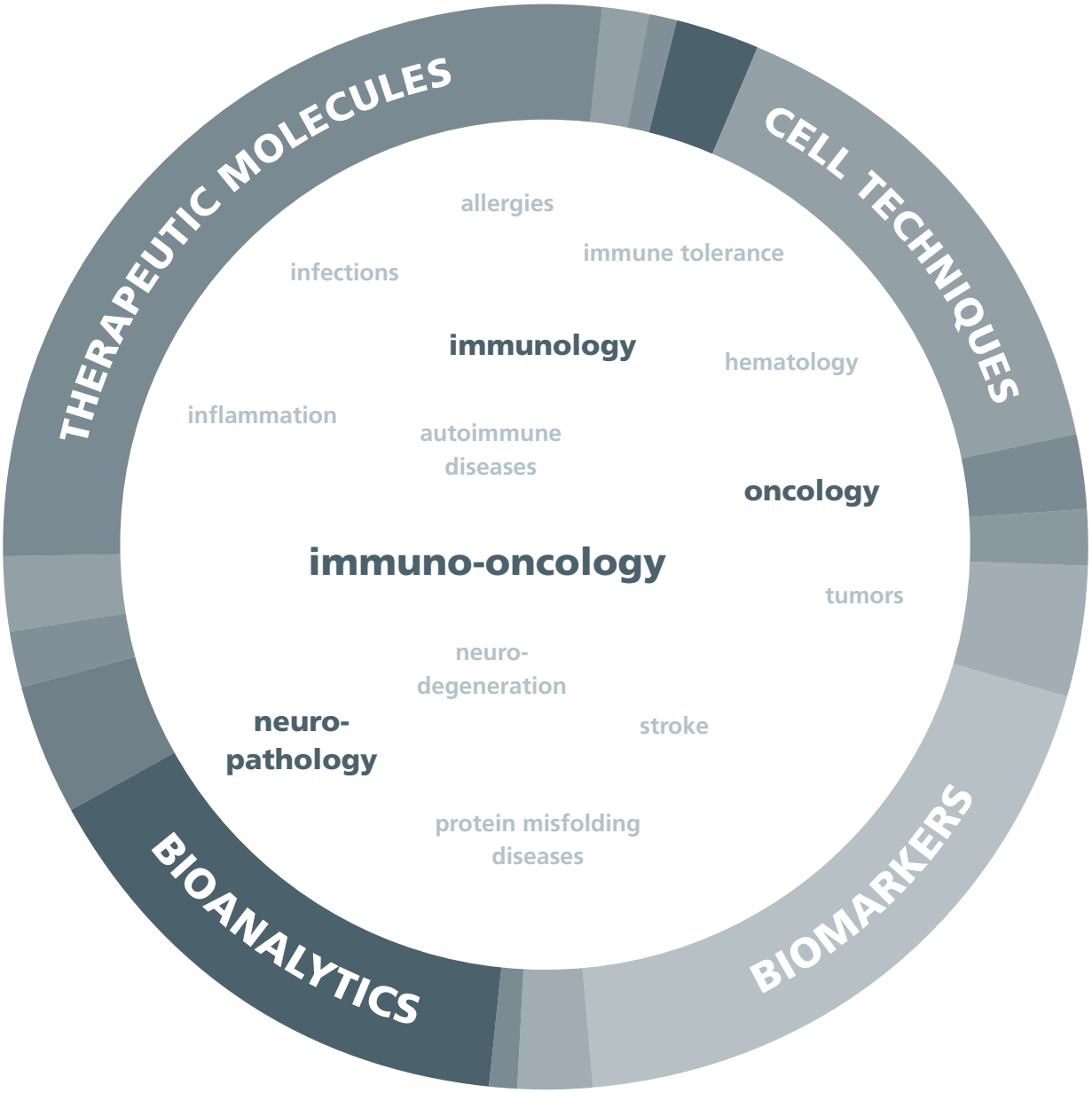
CELL AND GENE THERAPY

DRUGS & BIOLOGICALS

DIAGNOSTICS



COMPETENCIES AND INDICATIONS



KEY INSTITUTE FIGURES 2018*

PROJECT REVENUE

by funding agency

29.4 %
German national and regional government (TEUR 10 365)

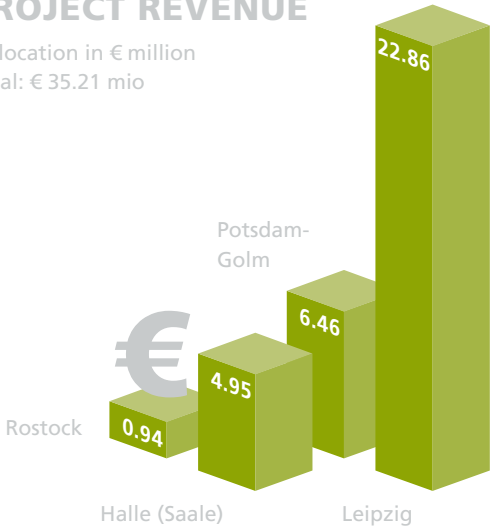
24.3 %
Other (TEUR 8 559)

0.4 %
EU (TEUR 142)

45.9 %
Industry (TEUR 16 143)

PROJECT REVENUE

by location in € million
Total: € 35.21 mio



EMPLOYEES

Workforce composition

53 %
Scientists incl. visiting scientists

7 %
PhD students

16 %
Technical assistants and laboratory technicians

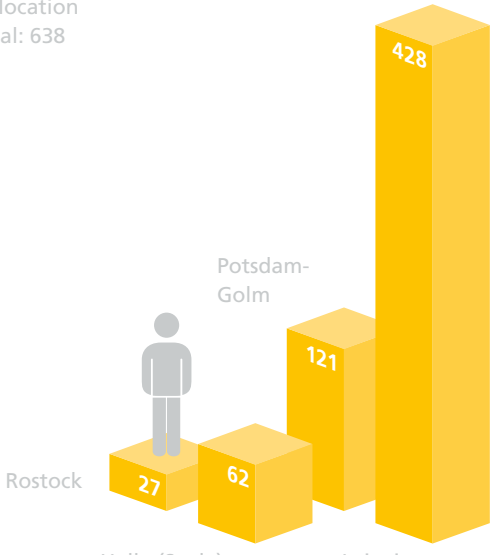
9 %
Student / scientific assistants

10 %
Administration / executive departments / IT and technical infrastructure

5 %
Interns / degree candidates / Bachelor students / Master students / trainees

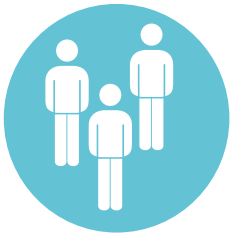
EMPLOYEES

by location
Total: 638



** Stand 31.12.2018*

SCIENTIFIC PRESENCE AND NETWORK 2018



68
Conventions and conferences

153
Industry partners

155
Research partners

235
Abstracts

89
Publications

13
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1
Book

11
Doctorates

11
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3
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117
Association memberships in various expert associations

33
Evaluator activities

40
Patent families

174
Patents and patent applications

63
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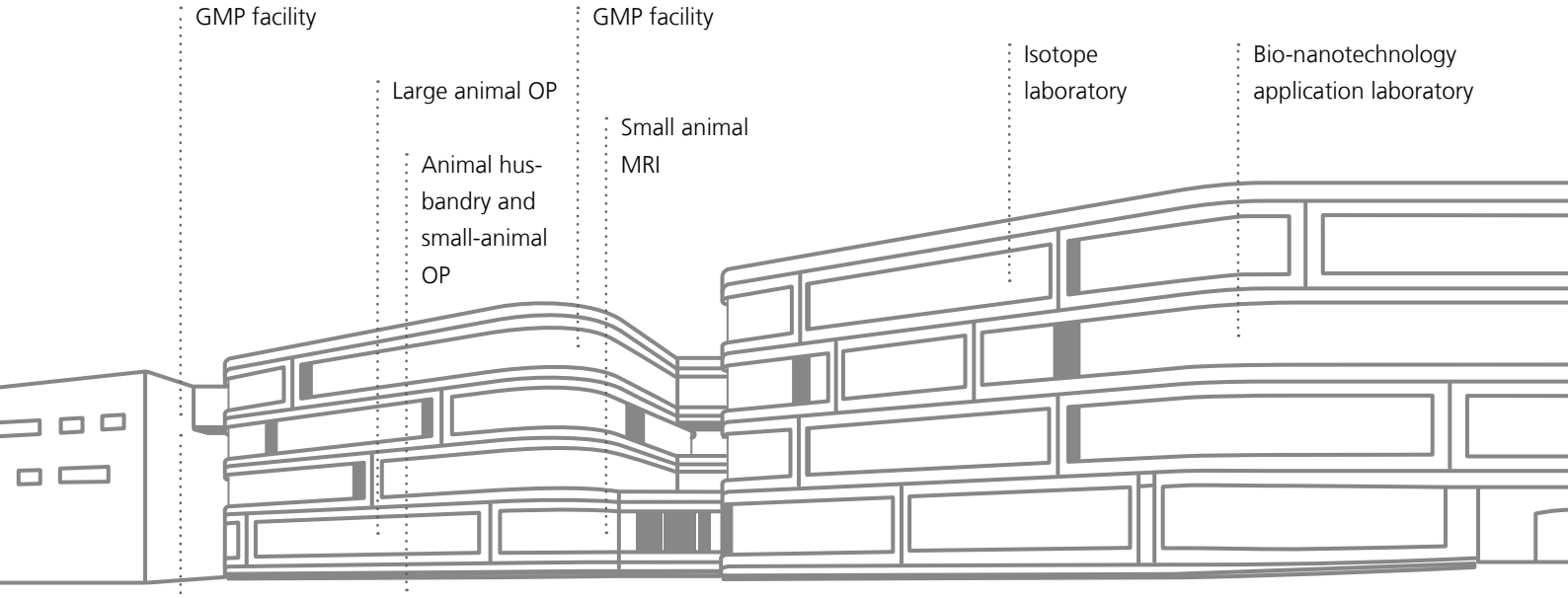
Detailed information on key figures and publications can be found in the full version of the annual report on pages 122–160.
http://s.fhg.de/etY

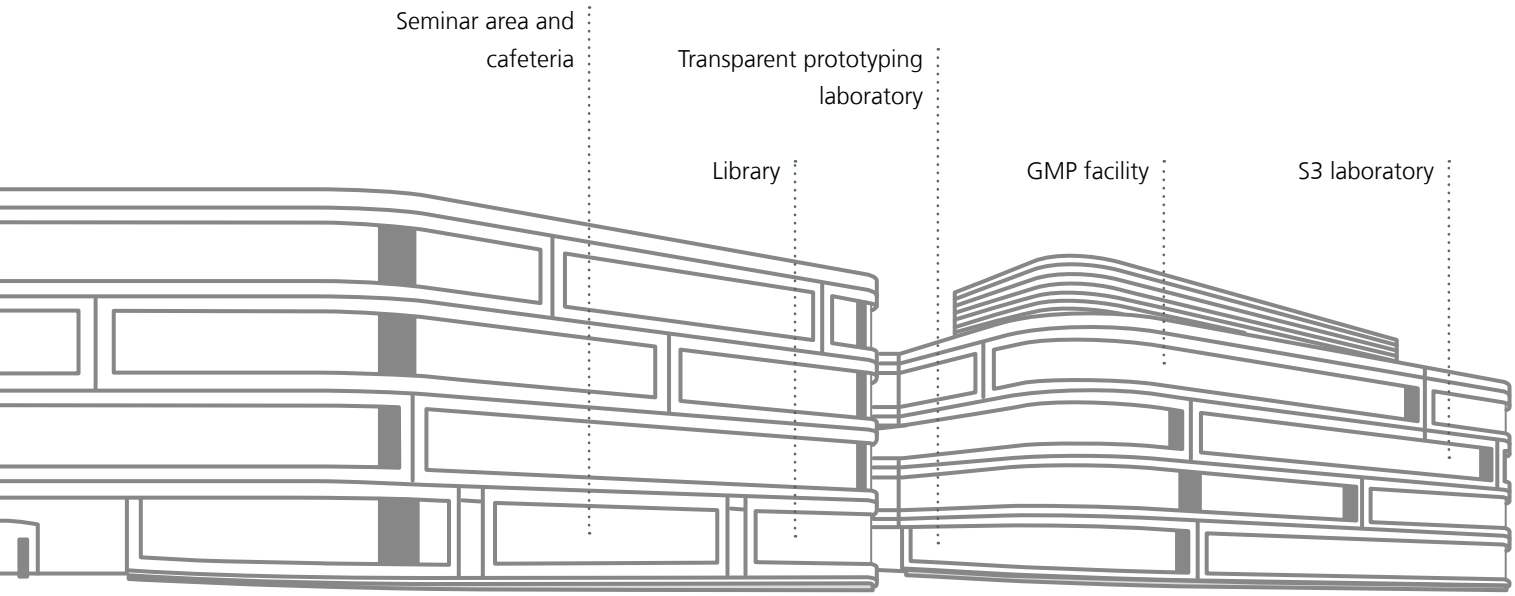
RESEARCH INFRASTRUCTURE AT THE LEIPZIG SITE



First extension building
Start-up operations: 2012 | Usable area: 1 568 m² | Lab space: 470 m² | Offices: 142 m² | Clean rooms: 410 m²

Main building
Start-up operations: 2008 | Usable area: 4 131 m² | Lab space: 1 867 m² | Offices: 1 615 m² | Seminar area: 276 m²

Rental area at BIO CITY Leipzig
Start-up operations: 2006 | Clean rooms: 334 m²



Second extension building
Start-up operations: 2015 | Usable area: 3 050 m² | Lab space: 1 171 m² | Offices: 881 m² | Clean rooms: 402 m²

DEPARTMENTS

MAIN DEPARTMENT OF GMP CELL AND GENE THERAPY

THE DEPARTMENT AT A GLANCE

The Main Department of GMP Cell and Gene Therapy operates three modern GMP facilities consisting of ten separate clean room suites (altogether 21 clean room grade B manufacturing rooms) which have been specially optimized for manufacturing of cell and gene therapy products, so called Advanced Therapy Medicinal Products – ATMP. The particular specialty of the about 130 highly qualified staff members is the GMP-compliant manufacturing and quality control of investigational medicinal products.

GMP-compliant process and quality control development as well as the creation of Standard Operating Procedures (SOPs) are intensively discussed with the project partner before being implemented. The leading staff in charge has many years of experience in designing GMP-processes in the cell and gene therapy area.

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PROJECT EXAMPLES

Manufacture of Kymriah®

The CAR-T cell therapy is a new type of cancer immunotherapy that uses the patient's own T cells to fight certain types of cancer. In order to do this, the cells are extracted in the clinic by leukapheresis before being genetically reprogrammed in vitro in such a way that they can use a chimeric antigen receptor to recognize cancer cells with a special antigen on their surface and initiate their destruction. This immunotherapeutic agent was manufactured for use in clinical trials on behalf of Novartis AG and approved by the European Commission for two indications in summer 2018.

BioBreast 1

Traditional reconstruction measures following a partial or full mastectomy are often accompanied by complications and side effects. The company BellaSeno® GmbH has developed an innovative technology that takes a patient-specific, bioresorbable polymer implant and fills it by injecting the patient's own body fat. These biodegradable breast implants are being produced under GMP conditions for preclinical trials in the Main Department of GMP Cell and Gene Therapy using a 3D printer.

autoCard study

The investigational medicinal product "CardAPcells" (cardiac-derived adherent proliferating cells) will be manufactured at Fraunhofer IZI in future in cooperation with Charité - Universitätsmedizin Berlin. The therapeutic agent contains special heart cells that are isolated from biopsy samples taken from the patient's own heart muscle and expanded over the course of a cultivation process lasting several weeks. Once clinical testing is complete, the new treatment method will be used in patients suffering from chronic myocardial insufficiency.

Further information on the department and its projects can be found in the full version of the annual report on pages 18–22.
http://s.fhg.de/Z3j

DEPARTMENT OF THERAPY VALIDATION

THE DEPARTMENT AT A GLANCE

The department was founded in January 2016 as a direct replacement of the former Cell Engineering/GLP unit. The main goal of the new department is the concentration of expertise for the preclinical validation of novel therapeutic approaches at IZI, to maximize the efficiency in developing new in vitro or in vivo models and their application in preclinical studies. Since the department manages the GLP test facility of Fraunhofer IZI, all preclinical studies (even those in other IZI departments) can be performed under GLP.

The department covers the following topics:

1) Planning and execution of preclinical efficacy and safety studies for new drug candidates (especially ATMPs) and medical devices (ISO 10993) under GLP or GLP-analogous conditions. This includes the development and validation of suitable in vitro and in vivo models.

2) Developing procedures for the diagnostic analysis of secretory and cellular protein biomarkers, including the development and production of specific monoclonal antibodies for their detection and finally the development and validation of the respective diagnostic assays (e.g. ELISA, lateral flow assays, Luminex®, flow cytometry).

3) Identifying and validating new protein biomarkers for diagnosis and therapy of chronic-inflammatory and tumor diseases, as well as for the sector of veterinary medicine / farm animal husbandry.

4) Developing human therapeutic monoclonal antibodies for the treatment of tumor and autoimmune diseases, as well as for passive vaccination against bacterial toxins and pathogenic viruses, and their advancement to drug candidates.

5) GMP-compliant production of clinical test samples, e.g. monoclonal antibodies (manufacturing authorization pursuant to Section 13 of the AMG obtained on July 12, 2018), in a separate clean room facility.

Units

- Preclinical Models, Dr. Ulla Slanina
- Protein Biomarker, Prof. Dr. Stefan Kalkhof
- Antibody Production, Dr. Maximilian Hoffmann

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PROJECT EXAMPLES

WormShield

Worm infections still present a huge medical challenge, especially in tropical and sub-tropical climate zones. A high number of parasites can already be treated with effective medication, but this is only possible based on an accurate diagnosis. This, in turn, generally requires well trained staff and a technical infrastructure that, in rural areas of developing and newly industrialized countries in particular, is not always available. Together with international partners, Fraunhofer IZI is therefore developing a rapid test for diagnosing hookworm infections that is easy to use, robust and sufficiently sensitive.

BioBreast 2

Traditional reconstructive measures following a partial or full mastectomy are often accompanied by complications and side effects. The company BellaSeno® GmbH has developed an innovative technology that takes a patient-specific, bioresorbable polymer implant and fills it by injecting the patient's own body fat. Preclinical safety tests are being conducted on the medical device in the GLP test facility in accordance with DIN EN ISO 10993.

Further information on the department and its projects can be found in the full version of the annual report on pages 23–28.
http://s.fhg.de/byU

DEPARTMENT OF IMMUNOLOGY

THE DEPARTMENT AT A GLANCE

Procedures to stimulate or suppress the immune system are developed in the Department of Immunology. These include vaccines on innovative technology platforms, e.g. novel inactivation methods or plasmid DNA. As such, efficient vaccines can be produced quickly and inexpensively. A further topic is improving the problem-free healing of transplants by the induction of specific tolerance. Furthermore, procedures are being developed to monitor immunoreactivity and to control dysfunctions such as graft-versus-host disease (GvHD). Bacteriostatic peptides and peptide banks for the analysis of immune reactions in food allergies are a further focus. Novel imaging procedures help analyze immunological and cell biological processes.

Units

- Vaccine Technologies, PD Dr. Sebastian Ulbert
- Immune Tolerance, PD Dr. Stephan Fricke
- Image Analysis of Cell Function, Prof. Dr. Ulf-Dietrich Braumann
- Preclinical Validation, Dr. Thomas Grunwald
- Ligand Development, Dr. Michael Szardenings
- Antimicrobial Agents, Dr. Andreas Schubert
- Biological Material Analytics, Dr. Juliane Spohn

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PROJECT EXAMPLES

Electron beams kill off pathogens

The Vaccine Technologies Unit has developed a new manufacturing process for inactivated vaccines based on low-energetic electron irradiation.

Preventing immunological complications following stem cell transplants

The main complication following allogeneic hematopoietic stem cell transplantation is acute graft-versus-host disease (aGvHD). An antibody-based treatment has been developed in the Immune Tolerance Unit that is expected to lessen or prevent this life-threatening immune reaction.

Non-destructive cell and tissue monitoring

In the Image Analysis of Cell Function Unit, an experimental imaging platform has been constructed and established based on light sheet microscopy (single plane illumination microscopy / SPIM). The imaging procedure is especially gentle on samples and allows living biological samples to be examined.

Mapping patient antibodies in serums

A new way of identifying antibody binding sites (epitopes) with greater precision, also directly from patient serums, has been designed in the Ligand Development Unit. The method is being applied, among other things, in a project identifying food allergies.

Fungicidal drugs from African medicinal plants

Plant-damaging fungi and their increasing resistances to traditional agents are becoming more and more of a problem in agriculture. In the Antimicrobial Agents Unit, active agents are being extracted from African medicinal plants and examined as to their fungicidal potential.

New drug against herpes

A treatment study is being carried out by the Preclinical Validation Unit to investigate a helicase-primase based drug for treating herpes simplex virus infections in the mouse model.

Further information on the department and its projects can be found in the full version of the annual report on pages 29–40.
http://s.fhg.de/c6a

DEPARTMENT OF CELL THERAPY

THE DEPARTMENT AT A GLANCE

The Department of Cell Therapy prepares new gene and cell therapy procedures for clinical application. This involves the validation of experimental approaches with an eye to safety, feasibility and efficiency. Numerous model systems that facilitate the preclinical testing of novel concepts under the strictest quality criteria have been and continue to be established by the department. These systems lend the obtained results a high level of predictive power with regard to their future clinical application. Cell therapeutic methods are used, for instance, in the case of ischemic diseases such as stroke and myocardial infarction while attention is also given to processes that could prevent cell degeneration and aging. The "sleeping" potential of stem cells is also investigated. Last but not least, the department focuses on cell therapy methods in the field of immuno-oncology, where genetically modified immune cells (cytotoxic T-cells) or natural killer cells (NK cells) are developed to treat tumors.

Units

- Experimental Imaging, Dr. Sebastian Greiser
- Cognitive Genetics, Dr. Arndt Wilcke
- Clinic Oriented Therapy Assessment, Dr. Antje Dreyer
- OpTcell, Dr. Jana Burkhardt
- Branch Lab Translational Cell Therapy, Dr. Stephan Klöß

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PROJECT EXAMPLES

Modern imaging procedures for diagnostics and preclinical research

Taking stroke research as an example, the Experimental Imaging Unit shows how the combination of different imaging procedures (including MRI, microscopy and laser scanning) can be used to collect detailed, quantifiable data.

LEGASCREEN

Development of a multimodal early-screening test to diagnose dyslexia. Genetic tests and specific brain activity measurements (EEG) are combined to draw conclusions on the development of dyslexia as early as preschool age and to recommend suitable support measures.

Evaluating therapeutic substances for transient stroke

On behalf of the company Omniox, the Clinic-oriented Therapy Assessment Unit is investigating the efficacy and safety of new treatment procedures for stroke in the sheep model. The aim is to minimize the consequences of a stroke and to extend the time window for administering further therapeutic measures.

Modified natural killer cells for treating cancer

On behalf of the company Affimed, the Translational Cell Therapy off-site unit in Hannover is developing a manufacturing procedure for natural killer cells that is intended to detect and destroy cancer cells via an antibody-mediated immune response.

Development of a therapy concept for neurodegenerative diseases based on the extracellular vesicles of mesenchymal stem cells

Exosomes are 30 to 90 nm large compartments (vesicles) that originate from a cell and are released into the extracellular environment. They contain molecules that are different to those the original cell, which enables them to "communicate" with other cells. This property makes them an interesting candidate for developing new therapies. Exosomes from mesenchymal stem cells are being investigated as to their potential to treat neurodegenerative diseases.

Further information on the department and its projects can be found in the full version of the annual report on pages 41–50.
http://s.fhg.de/v8h

DEPARTMENT OF DIAGNOSTICS

THE DEPARTMENT AT A GLANCE

The Department of Diagnostics offers a value chain that comprises the screening and testing of biomarkers, bioinformatic analysis and interpretation of complex transcriptome and genome data ("big data"), development of in vitro diagnostics (IVD) and point-of-care platforms as well as appropriate preclinical animal models.

Within the department, the RIBOLUTION Biomarker Center was established in the course of the Fraunhofer-Zukunftsstiftung- (Future Foundation-) funded consortium RIBOLUTION (RIBOnucleic acid-based diagnostic soLUTIONs) to systematically identify and validate novel diagnostic or prognostic biomarkers. Noncoding RNAs that possess a promising and long underestimated biomarker potential are a particular focus. The RIBOLUTION Biomarker Center provides experienced bioinformatics for analyzing NGS and other complex data sets. Competencies in study and data management serve to design and conduct clinical cohorts as well as to manage clinical and experimental data. For the development of diagnostic assays, a quality management system following DIN EN ISO 13485 rules has been implemented.

The development of innovative molecular diagnostic test systems is offered for medical and food applications and comprises PCR- and NGS-based IVDs, lab-on-a-chip-platforms, and strip-based flash tests. The department aims at diagnostic solutions in many clinical fields, including cancer, infectious and inflammatory diseases.

It also offers the development of companion diagnostics and provides many established cell and animal models in various areas like tumor stem cells, rheumatoid arthritis and other chronic-inflammtory diseases as well as many more. Furthermore, xenogene transplantation models serve to close the gap between model and patient.

Units

- Inflammation Models and Immunodiagnostics, Dr. Franziska Lange
- MicroDiagnostics, Dr. Dirk Kuhlmeier
- Tumor Stem Cells, Dr. Peter Ruschpler
- DNA Nanodevices, Dr. David M. Smith
- CardiOmics, Prof. Dr. Dr. Dr. Andreas Oberbach
- RNA Biomarker, Dr. Sophie Bartsch
- Next Generation Diagnostics, Dr. Conny Blumert
- Bioinformatics, Dr. Kristin Reiche
- Study and Quality Management, Dr. Catharina Bertram

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PROJECT EXAMPLES

Establishing a model for chronic kidney disease (CKD)

On behalf of Fresenius Kabi, an animal model has been developed to test the safety and efficacy of medicinal and dietary therapies for chronic kidney disease.

Development of novel biomarkers to diagnose and predict prostate cancer

As part of the RIBOLUTION project, funded by the Fraunhofer Future Foundation, new biomarkers were identified for prostate cancer based on transcriptome-wide (RNA) sequencing together with microarray analyses and bioinformatic evaluations. Biomarkers were identified here that can diagnose the disease and also predict the aggressiveness of the cancer.

Pinpointed stimulation of EphA2 receptors via DNA-templated oligovalence

In DNA nanotechnology, DNA strands are used not for their genetic coding abilities but as a construction material. Based on rational design principles, individual DNA strands can be assembled into precise nanostructures of almost any form. These nanostructures facilitate the accumulation of functional molecules such as peptides at almost every distinct position along its structure. Taking the stimulation of EphA2 receptors as an example, the project shows that simple DNA structures can be used to significantly increase the efficacy of weak peptides while using an oligovalent arrangement in the nanometer range.

Predictive biomarkers for prostate cancer

Transcriptome-wide analyses are being conducted to clarify the underlying molecular mechanisms of prostate cancer in order to recognize and predict the disease at an early stage.

Further information on the department and its projects can be found in the full version of the annual report on pages 51–60.
http://s.fhg.de/Z48

DEPARTMENT OF EXTRACORPOREAL IMMUNOMODULATION

THE DEPARTMENT AT A GLANCE

The department focuses on the development and evaluation of extracorporeal (outside the body), organsupporting technologies with a particular emphasis on supporting the immune system. We offer the full range of preclinical and clinical analyses of extracorporeal technologies based on a broad spectrum of in vitro simulations, animal models, as well as a powerful clinical study network for in and out-patients. Moreover, we offer self-developed unique analytic and diagnostic devices including an ex situ intestinal model, a cell sensor and novel protein assays.

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PROJECT EXAMPLES

Cryoregeneration of dialysis water

Patients whose bodies have a weakened detoxification function due to a late-stage chronic kidney disease regularly need to have dialysis. Due to the frequent and time-intensive outpatient treatment, this procedure, which is essential for the patient's survival, is associated with enormous limitations in terms of quality of life and mobility. This is why the EXIM off-site unit is working on a way to make dialysis mobile.

Further information on the department and its projects can be found in the full version of the annual report on pages 61–63.
http://s.fhg.de/xhU

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION

THE DEPARTMENT AT A GLANCE

The Department of Drug Design and Target Validation in Halle (Saale) boasts considerable expertise in various areas of preclinical drug development, placing a special focus on neurodegenerative and inflammatory diseases. The department's work covers almost the entire range of activities associated with the early stages of drug development, from identifying and characterizing target proteins to identifying initial drug candidates right over to testing substances in the animal model. Members of staff at the Halle (Saale) branch are characterized by their extensive experience in industrial and pharma-relevant research. This allows scientific issues to be tackled on behalf of industry partners on the one hand, and new drugs and target proteins from the institute's own preliminary research to be identified, patented and subsequently form the basis of industry cooperations on the other.

Small molecules and biologicals will be developed and tested on the back of the department's new treatment concepts. Alongside this, testing procedures will be developed for the identification and diagnostic application of biomarkers, which allow the course of both the disease and therapy to be monitored. Furthermore, the department also houses the expertise required to create pharmacologically relevant in vitro and in vivo models.

Besides modern peptide synthesis and protein analytics methods (MALDI-TOF and LC-MS), the department has also developed a broad spectrum of biophysical methods for characterizing therapeutically relevant metabolic pathways, whose key proteins as well as cell-based and pharmacological models are used to characterize innovative chemical and biological agents.

Units

- Molecular Biotechnology, Dr. Holger Cynis
- Protein and Drug Biochemistry, Dr. Stephan Schilling
- Drug Design and Analytical Chemistry, Dr. Mirko Buchholz
- Protein Misfolding Diseases, Dr. Anja Schulze

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PROJECT EXAMPLES

Antibodies for treating neurodegenerative diseases

A number of neurodegenerative diseases are primarily caused by the depositing of defective proteins The Protein and Drug Biochemistry Unit is developing therapeutic antibodies that prompt the immune system to break down these protein aggregates, which is expected to result in a curative therapy.

Determining the pharmacokinetic parameters of small molecules

A vital part of developing new drugs is characterizing them in terms of liberation, absorption, dispersion, metabolism and excretion (L-ADME parameter) in the animal model. This is intended, in particular, to provide information on the overall exposure of the organism, bioavailability following application and the half-life period of the active agent in the circulation. To assist with this, a catheter-based test procedure was established in the Molecular Biotechnology Unit to determine pharmacokinetic properties of small molecules in rats. The procedure is being used in the development of new drugs, for instance to treat neurodegenerative and inflammatory diseases.

Broadening the chemical space of metal binding groups

By drawing on computational chemistry procedures, the Drug Design and Analytical Chemistry Unit is supporting the development of new drugs whose target structures are metal ions in the catalytic center of enzymes. The procedure helps to identify specially tailored molecules which will then form the basis of manufacturing drugs with as specific an effect as possible.

Further information on the department and its projects can be found in the full version of the annual report on pages 64–70.
http://s.fhg.de/cQ2

DEPARTMENT OF BIOSYSTEM INTEGRATION AND PROCESS AUTOMATION

THE DEPARTMENT AT A GLANCE

The department delivers solutions for complex laboratory automation tasks in biotechnology.

Work here focuses on processes related to bioanalysis, diagnostics and cell culture, expansion, preparation and monitoring and aims at increasing the efficiency, quantity and quality of laboratory processes including cell products.

A further focal area is found in developing procedures and devices for a broad range of point-of-care applications. Among other things, an in vitro diagnostics (ivD) platform is available for this purpose, which can be adapted to different diagnostic tests depending on the task at hand.

Furthermore, procedures and devices are also available for analyzing and using molecular interfaces and higher-order electronic effects. Special importance is also assigned to developing procedures to gently dehydrate and fix dry reagents, which are used in all variants in diagnostics and analytics.

Units

- iVD Platform / PoC Technologies, Dr. Harald Peter
- Biomolecular Nanostructures and Measurement Technology, PD Dr. Ralph Hölzel
- Biomimetic Functional Materials, Dr. Nenad Gajovic-Eichelmann
- Laboratory and Process Automation, Jörg Henkel

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PROJECT EXAMPLES

Peptide-decorated biomimetic surfaces for typing influenza viruses

Based on short, linear peptides used as specific recognition molecules, a novel system for subtyping influenza viruses is being developed in cooperation with the Robert Koch Institute and the University of Potsdam.

Further information on the department and its projects can be found in the full version of the annual report on pages 71–75.
http://s.fhg.de/2iM

DEPARTMENT OF MOLECULAR AND CELLULAR BIOANALYTICS

THE DEPARTMENT OF A GLANCE

The department is devoted to developing systems to detect, analyze and process challenging biological samples. These systems address demands in the fields of biomedicine, diagnostics, biotechnology, process control as well as environmental analytics, food safety and animal husbandry. The spectrum of solutions ranges from stand-alone sensor and fluidic components to integrated analysis systems and comprehensive database tools. The development of point-of-care tests, e.g. for drugs and serum screenings, forms as much a part of the unit's scope of activities as establishing assays for the validation of biomarkers. Lab-on-a-chip systems for cultivating, processing and analyzing cell samples present a further focus. These chips allow long-term cultivation and toxicity tests on suitable cell clusters and micro-precise positioning of single cells or sorting heterogeneous cell populations. All of the department's activities are based on its profound expertise in sensor technology, spotting and dispensing technologies, surface coatings, microfluidics and the integration of functional units into all-in-one solutions. Its competence in molecular and cell biology allows the department to use its technological abilities in the most purposeful manner. Work can be carried out efficiently using the state-of-the-art instruments and facilities available in the department's well-equipped laboratories.

By integrating biobanks into so-called metabiobanks, the department provides solutions that facilitate and support the web-based case-by-case and sample-by-sample search for human biospecimens and associated data across institutional and national borders.

Units

- Microarray and Sensor Technology, Dr. Eva Ehrentreich-Förster
- Biomarker Validation and Assay Development, Dr. Harald Seitz
- Molecular Bio-Engineering, Dr. Markus von Nickisch-Rosenegk
- Microsystems for In Vitro Cell Models, Dr. Katja Uhlig
- Microfluidic Cell Processing and Cell Analytics, Dr. Michael Kirschbaum

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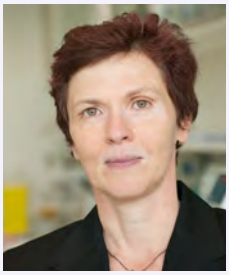

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PROJECT EXAMPLES

Particle-based sensors as substrates for gently expanding high-quality cell samples

Thermoresponsive polymer coatings are used to break up cell-surface contacts to obtain cells when cultivating adherent cells. Structural changes induced by a change in temperature can then be used in these polymers to manage cell adhesion on the layers. Compared to conventional procedures that use digestive enzymes or mechanical forces, this procedure is noninvasive and therefore much gentler on the cells. The integration of microsensor particles also allows various parameters to be monitored in real time.

Microstructured cell culture substrates for controlling neuronal cell growth in vitro

A cell cultivation substrate microstructured with thermoresponsive polymers is being developed using micro-manufacturing technologies. This will form the basis of the targeted cultivation of defined neuronal networks and their analysis. It can be used to control not only the cells but also the orientation of the growing neurites, and therefore to manage how the cells connect to each other.

Further information on the department and its projects can be found in the full version of the annual report on pages 76–82.
http://s.fhg.de/MiR

DEPARTMENT OF CELL-FREE AND CELL-BASED BIOPRODUCTION

THE DEPARTMENT AT A GLANCE

Conserving resources and creating efficient material cycles are two challenges currently facing the economy and technology. The sufficient and affordable availability of high-quality synthetic products is an important basis for making progress here, especially in the field of health care. Active agents and analytes, biomolecules such as enzymes, antibodies and aptamers often form the basis of drug development in terms of diagnostics and therapy. But also in food and environmental technology, in the agricultural, cosmetics and detergent industries, the need for synthetic biomolecules is constantly on the rise. At present, many of these substances are manufactured using living cells and organisms. However, this is subject to considerable limitations. A sizable material and energy input has to be made to preserve cell metabolism itself. Beyond this, many metabolites, by-products and proteins, also in higher concentrations, are toxic to cells or organisms and can impede or even prevent these substances from being manufactured cost-effectively.

The cell-free bioproduction of high-quality proteinogenic biomolecules opens up completely new possibilities here. By using only the subcellular components of the organisms required for synthesis it is possible, in suitable reaction environments, to efficiently manufacture biomolecules with complex and also completely new properties. The technologies established at the Potsdam-Golm site allow these procedures to be used in an economically efficient way, thus creating a new basis for the economic production of active proteins.

The development, synthesis and also transfer of functional nucleic acids such as aptamers into market-relevant applications are just as much a focus as the analysis of cold-adapted snow algae in extremophile research. The latter of these are being used to extract high-quality substances such as antioxidants or fatty acids and are being manufactured in photobioreactors. The CCCryo culture collection is a unique bioresource that can be used by interested academic and private enterprise groups.

Units

- Functional Nucleic Acids – Aptamers, Dr. Marcus Menger
- Eukaryotic Lysates, Doreen Wüstenhagen
- Extremophile Research & Biobank CCCryo, Dr. Thomas Leya
- Cell-free Protein Synthesis, Dr. Stefan Kubick

Contact

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PROJECT EXAMPLES

Evaluating protein synthesis in cell-free systems

Various cell-free systems are being investigated and evaluated for different scientific issues. Special requirements such as glycosylation, membrane protein synthesis in the native environment, disulphide bridging or even signal sequence dissociations are being focused on in the multiphased evaluation.

Cell-free synthesis and functional characterization of membrane proteins

Membrane proteins are addressed by a number of pharmaceuticals and exhibit a great deal of potential for future drug development. Synthesizing these proteins in cultivated cell lines, however, is often associated with huge difficulties, especially in terms of achievable protein yield, solubility, feasibility of protein purification, manifestation of cytotoxic effects as part of protein expression in cells and also functionality. Cell-free systems on the other hand present open systems that are largely controllable and can specifically ensure optimal reaction conditions.

Aptamer-based biomarker assay developments for the early recognition of bladder cancer

A diagnostic procedure is being developed to identify bladder cancer in urine samples. The test is based on aptamers (short, single-stranded DNA or RNA molecules) that recognize and bind specific marker proteins for bladder cancer. The test is expected to improve the early detection of this type of cancer in the long run.

From alga of the year 2019 to the genome of cold-adapted snow algae

Genetic research is being conducted into cold-adapted algae that thrive in Arctic regions under hostile environmental conditions (cold and freeze stress, light and UV stress, salinity and drought stress) in order to understand their defensive mechanisms. Work here is focused around enzymes of industrial interest that could be applied in food processing, UV protection and cryoprotection, for cosmetic products or even as a special enzyme for diagnostic laboratory applications.

Further information on the department and its projects can be found in the full version of the annual report on pages 83–90.
http://s.fhg.de/v9H

CENTRAL FACILITIES AND SERVICES

GLP TEST FACILITY

Good Laboratory Practice (GLP) describes a quality assurance system for conducting safety tests on chemicals, drugs, pesticides and food additives. It regulates the implementation, documentation, archiving and reporting of respective tests.

Fraunhofer IZI has been certified as a GLP test facility since 2009. The facility plans and conducts preclinical efficacy and safety studies for new drug candidates (especially ATMPs) and medical devices (ISO 10993) under GLP and GLP-analogous conditions. This involves developing and validating suitable in vitro and in vivo models. The test facility boasts a state-of-the-art setup for keeping small animals as well as small and large animal operating rooms. Furthermore, a broad spectrum of validated SOPs are implemented here for equipment and methods.

The test facility is currently certified for testing category 9. This includes, among other things, safety testing for ATMP immunotoxicity / immunogenicity, biodistribution and tumorigenicity in vitro and in vivo.

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GMP MANUFACTURING

GMP (Good Manufacturing Practice) describes a set of quality assurance guidelines for production processes and spaces with regard to drugs manufacturing. It regulates, among other things, the requirements concerning hygiene, facilities, equipment, documentation and controls.

Fraunhofer IZI assumes the manufacture of investigational medicinal products for clinical trials. Manufacturing capacities here range from therapeutic antibodies over to so-called advanced therapy medicinal products (ATMPs). These include cell-based drugs such as cell, gene and immune therapeutics as well as tissue engineering products.

Antibodies

In recent years, the increasing number of therapeutic monoclonal antibody (mAb) candidates under preclinical and clinical development have required new flexible, efficient, and economic opportunities for GMP production of therapeutic antibody candidates. Small-scale batch production of test samples for late preclinical GLP animal studies or for phase-1 and phase-2 clinical studies is often not appropriate for large-scale manufacturing facilities in the industry.

The clean rooms used for antibody production cover a total area of 180 m² and comprise all clean room categories from D to A. The use of single-use equipment and materials enables an easy adaption to new process requirements. The GMP facility can be used for different contract manufacturing processes for preclinical and clinical (Phase 1/2) test samples as well as for process or instrument validation projects under consideration of special customer requests. The standard equipment can be easily adapted for new products.

The manufacturing team's portfolio includes transferring biopharmaceutical candidates from preclinical research into clinical development, drafting user-specific processes and manufacturing e.g. human monoclonal antibodies on a 200 L scale in compliance with GMP.

In summary the main advantages are:

- High flexibility
- Easy switch to different products
- Fast implementation of technology changes
- Customized production
- Ideal batch size for preclinical and early clinical trials
- Possibility to obtain ready-to-use GMP-compliant products by integrated sample filling

Contact

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Advanced Therapy Medicinal Products (ATMPs)

The Fraunhofer IZI maintains three GMP-compliant clean room facilities. Through the flexible design, the facilities are especially attractive for new biotechnology companies that seek to bring newly developed medicinal products into clinical application via clinical trials. The facilities are divided into different independent suites. Each has its own grade C clean rooms (preparation), own air locks from grade C to B (personnel and materials transfer) and two grade B rooms (aseptic manufacturing). The clean room grade A is provided via laminar airflow cabinets that are installed in the B-rooms. The available clean room suites are specialized in conducting processes for manufacturing human autologous and / or allogeneic cell and gene therapeutic products (advanced therapy medicinal products). In addition to the clean rooms and the technical infrastructure, the Fraunhofer IZI offers assistance for the set-up and validation of GMP-compliant manufacturing processes as well as for obtaining a manufacturing authorization pursuant to section 13 of the German Drug Act (AMG).

Why are GLP and GMP important?

The clinical trial of new drug candidates is an essential step on the way to approval. Since the 12th revision of the "Arzneimittelgesetz AMG" (German Drug Act) every clinical drug trial must be approved of by the responsible higher federal authority ("Bundesinstitut für Arzneimittel und Medizinprodukte", Federal Institute for Drugs and Medical Devices, Paul-Ehrlich-Institut) and by the responsible ethics committee prior to the initiation of the clinical study. In order to obtain this authorization, the efficacy and safety of the investigational medicinal product must first be verified within the framework of GLP-compliant preclinical investigations (e.g. toxicological testing procedures). Furthermore, the quality of manufacture of the investigational medicinal products must be verified by a GMP manufacturing authorization pursuant to § 13 AMG. Relevant trial results from GLP-certified trial institutions and a GMP manufacturing authorization are thus absolutely prerequisite when applying for the clinical trial of a new medication.

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IMAGING

Phenotyping biological samples using multiple imaging methods forms a core competence of preclinical research. This enables thorough depiction, from the smallest structures (cell organelles) right through to entire organ systems, both in spatial and temporal resolution (4D).

Fraunhofer IZI has access to a comprehensive, state-of-the-art equipment pool that enables the acquisition and evaluation of various (also correlative) image data. Partners and customers are advised on biological, technical and economic matters and supported in carrying out and evaluating experiments. Furthermore, experimental procedures and equipment can be used, adapted and developed.

In vivo imaging

Magnetic resonance imaging (7 Tesla high-field small animal MRI) (image 1)

- Examination of soft tissues and organs, use of contrast agents and cell labeling possible, long-term measurements in single individuals
- Depiction of anatomical changes, MRS, diffusion methods, functional imaging

Computer tomography (CT and X-Ray for small animals) (image 2)

- Depiction of dense (bone, cartilage) and contrast-enhanced (soft tissue) structures
- 3D data sets can be used for conformal radiation treatment planning

Fluorescence and bioluminescence imaging for small animals

- Monitoring tumor growth and progression of inflammation, tracking cell movements following transplantation (cell tracking)
- Complex reconstruction of in vivo parameters by means of fluorescent imaging tomography (FLIT) or, in the case of bioluminescent sources, by means of diffuse light imaging tomography (DLIT) and spectral unmixing

Bedside imaging for small animals

- Various ultrasound units with a number of transducers and an implemented Color Doppler
- Flexible miniature cameras for the routine endoscopic examination of small animals and for the development of new lens attachments

In vitro / ex vivo imaging

Clearing tissue samples

- Preparing samples for imaging (especially 3D fluorescence microscopy)
- Enabling detailed images of deeper layers of the sample that are usually only visible through histological sections

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Confocal laser scanning microscope with live cell imaging

- Analysis of cell cultures and tissues in 4D, localizing target structures inside cells
- Standard laser lines from blue to red, water immersion lenses, real-time rendering and quantification of results

Light sheet microscopy

- Flexible light sheet microscope with modular sample chamber for sample sizes from just a few µm to 2 cm
- For the study of light-sensitive live-cell samples in high temporal resolution

Atomic force microscopy

- Nanometer-scaled, micro-mechanical sampling of surfaces using a cantilever measuring needle and measurement of the occurring atomic forces

MALDI Mass Spectrometry Imaging (MALDI-MSI)

- Label-free methods of depicting the distribution of macro molecules in histological samples based on their degree of ionization and time of flight (TOF) in the electric field; special sample preparation and matrix application required, statistical evaluation of distribution patterns

Laser capture microdissection

- Isolating individual cells or tissue structures by means of microscopic laser cuts, analyzing samples using molecular biology methods (RT-PCR, proteomics)

Hardware-linked evaluation process

- Stereological quantification using the upright fluorescence and reflected-light microscope for unbiased histological evaluations
- Virtual microscopy in order to create completely virtual tissue sections for digital post-processing, high-throughput technique

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CENTER FOR EXPERIMENTAL MEDICINE

The development of new drugs entails testing using suitable animal models. Animal experiments are therefore an integral component in the development of new drugs, therapies and diagnostic procedures. The institute's Centre for Experimental Medicine (TEZ) is a central unit which facilitates important steps in translating research findings into a clinical application for human subjects.

Moreover, the institute has access to one of the most state-of-the-art animal houses in Germany. The TEZ is distinguished by its highly technical facilities, which are optimized to handle preclinical research projects. These facilities include modern rooms in which the animals are kept, featuring standardized hygiene levels and individually ventilated cage systems that are monitored via the building management system.

The health and care of the animals is of the highest priority. Highly qualified personnel support the scientific staff in daily care, health monitoring and breeding activities, and in administering treatments.

All experimental work can be carried out under practically sterile conditions. Several fully fitted operating suites allow small and large animals to be examined and treated. The comprehensive, state-of-the-art equipment guarantees correct anesthesia, analgesia and species-relevant blood analyses.

An expansive equipment pool for imaging technologies at the institute enables partly non-invasive analysis methods and also contributes towards reducing the need for animal experiments. This means, for example, that in vivo imaging analyses can be carried out using, for instance, 7 Tesla magnetic resonance imaging, bioluminescence imaging or small-animal CT.

In order to work on a range of issues, the TEZ has access to areas approved for genetic engineering safety levels S1 to S3; it may also conduct in vivo studies in line with GLP (Good Laboratory Practice).

The TEZ forms the central interface at the institute for processing preclinical development projects. Furthermore, cooperation projects with external clients and other research institutes are also carried out. At the same time, the TEZ acts as a training facility for animal care supervisors in a research and clinical setting, also offering advanced training courses for experimenters.

Adherence to the animal welfare guidelines is strictly monitored by the institute's animal welfare officers and regularly controlled by the regional animal welfare authority.

Equipment and services:

- Small animals are kept under state-of-the-art standards and permanently monitored
- Animal husbandry under GLP standards
- Animal husbandry with the option to use infecting agents for experimental infection

- Quarantine services
- Standard in-breeding and breeding transgenic lines
- Operation units in various areas including provision of inhalation anesthesia for small and large animals

- Large-animal OP area with intensive care capacity
- C-arm
- Option for individual stereotactic brain surgery
- Autopsy room for large animals
- Intraoperative blood gas analyses

- Small animal endoscope
- Blood cell meter
- Surgical microscope
- Stereotactic manipulation
- Temperature control during operations

- In vivo bioluminescence
- Small animal magnetic resonance imaging
- Small animal computer tomography
- X-ray unit for whole-body irradiation and pinpointed radiation therapy
- Large capacity autoclave
- Sterilization units using hydrogen peroxide fumigation
- Cryopreservation of spermatozoa and embryos
- Tissue bank

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RIBOLUTION BIOMARKER CENTER

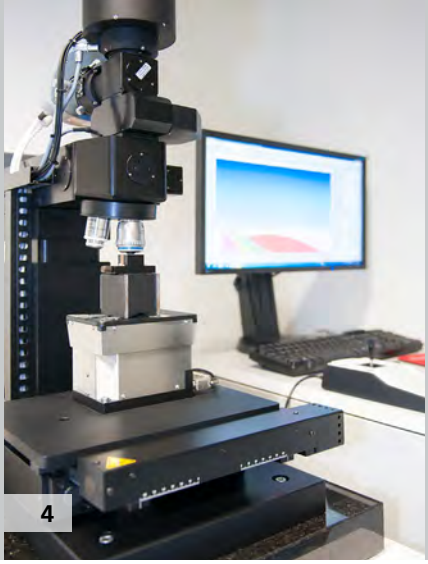
Over the past few years, the Fraunhofer Future Foundation has supported the RIBOLUTION project consortium, which takes an innovative approach to identifying new biomarkers for modern diagnostic solutions. The RIBOLUTION Biomarker Center was set up as part of a close cooperation involving five Fraunhofer institutes and several universities. It was opened on April 26, 2016, at the Fraunhofer Institute for Cell Therapy and Immunology IZI in Leipzig.

At the RIBOLUTION Biomarker Center, novel biomarkers are identified based on ribonucleic acids and developed through to clinical "proof of concept" with the aid of selected patient cohorts. At present, activities are primarily focused on development programs in the areas of prostate cancer, chronic obstructive pulmonary disease (COPD) and infectious diseases.

Biomarker screening and validation

By integrating state-of-the-art genomic analysis methods such as next-generation sequencing (NGS) using our own bioinformatical data analysis methods developed in house, the RIBOLUTION Biomarker Center is able to identify biomarkers and develop new diagnostic tests at the **highest technological level**:

- Illumina HiSeq and Miseq (image 1): Ultra-high-throughput sequencing platforms
- Hamilton Microlab STARlet/STARplus (image 2): Fully automated preparation of samples for sequencing and fully automated extraction and purification of nucleic acids
- Agilent microarray scanner (image 3)
- EMD (image 4): Quality and quantity analyses of minimal amounts of nucleic acids with high sensitivity; developed by Fraunhofer FIT
- QIAcube (image 5): Semi-automated extraction and purification of nucleic acids
- RiBOT (image 6): Novel procedure for the automated validation of biomarkers in high-throughput based on complex interactions between actuator engineering and media to be dispensed; developed by Fraunhofer IPA



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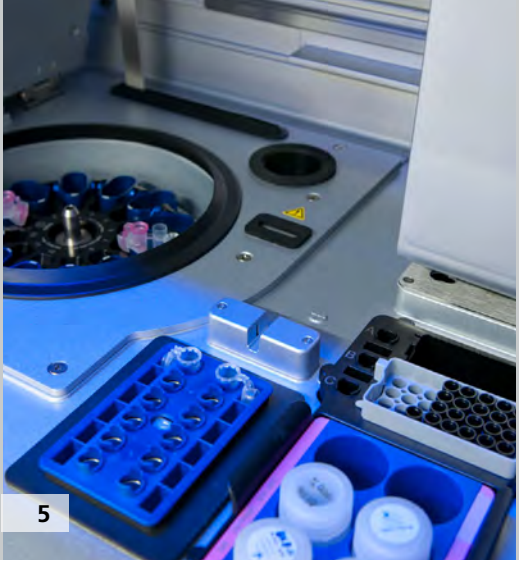

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The highest quality standards are defined and implemented from start to finish, which increases the intrinsic value of the obtained data and lays the foundations for the implementation of a quality management system pursuant to DIN ISO 13485, which will become necessary as the project progresses.

New biomarkers are identified and validated using bioinformatical methods. This includes designing custom expression microarrays and analyzing expression microarray data. A proprietary data management system has been developed to store and supply all clinical and experimental data and is used to manage the extensive biobank which has emerged in the RIBOLUTION project.

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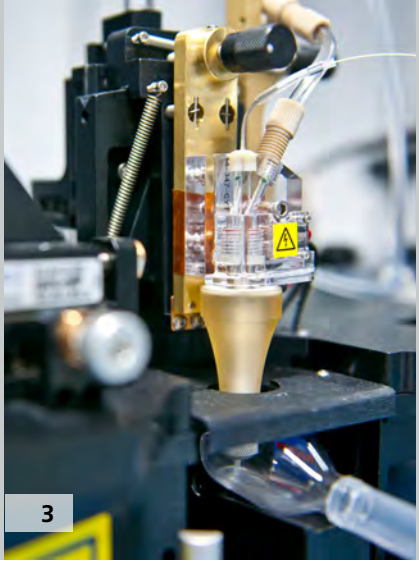

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BIO-NANOTECHNOLOGY APPLICATION LABORATORY (BNAL)

The Bio-Nanotechnology Application Laboratory (BNAL) in Leipzig represents a research infrastructure jointly run by Fraunhofer IZI and Fraunhofer IKTS. With this laboratory, both institutes are opening up new fields of application in biomedicine related to various nanotechnologies.

State-of-the-art equipment allows biological and medical issues to be handled in an interdisciplinary manner. BNAL provides research and development services from fundamental biomedical research by process development up to the development and validation of innovative technologies and system solutions.

Biological and medical expertise at Fraunhofer IZI (e.g. oncology, chronic inflammatory diseases and neuro-degenerative diseases) in combination with established analysis methods for material diagnostics at Fraunhofer IKTS enable the development of new diagnostic and therapeutic technologies and procedures.

Imaging procedures

- Optical coherence tomography (image 1): Uses near-infrared light to depict the internal and surface structures of various materials in high resolution.
- Multi-acousto-scope: The combination of three microscopy techniques paves the way to innovative new examination strategies.

Cell characterization and classification

- Diagnosis and mapping for cell biology studies: Non-intrusive way of delivering high-resolution, geometric information from the inside of test objects.
- Ultrasound broadband spectroscopy system: This procedure has long been used in the medical diagnosis of cell tissues, biological materials and in the analysis of fluid media. It mainly identifies acoustic and mechanical properties of substances.
- High-throughput flow cytometry (image 2): Rapid, multiplex, high-throughput screening of cells and beads in suspension.
- Fluorescence relaxation for characterizing cells in flow cytometry as a new, label-free procedure that will also be used to characterize cell therapeutic agents and which will be tested on a BD Influx high-throughput cell sorter (image 3).

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Surface sterilization and modification

- Electron beam dosimeter (image 4): Dose measurement of highenergy radiation (e.g. gamma or electron radiation) on even on the different positions of bent 3D free-form surfaces.
- System for electron irradiation of surfaces: Sterilization of package / surfaces, inactivation of microorganisms for vaccine production or targeted adjustment of material properties by means of electron irradiation.

Nanotechnology

- Droplet digital PCR system: PCR-based, absolute quantification of microbial / viral or eukaryotic DNA / RNA as well as precise detection of low genome copy numbers.
- Zetasizer: Determination of particle and molecule sizes, e.g. for characterizing recombinant proteins, micelles and
- nanoparticles.
- Micro-spotter unit (image 5): Automated dosing of tiny quantities of liquid (e.g. biological or organic solutions, or solutions containing nanoparticles) on a broad range of different surfaces for the production of microarrays.
- Hot-embossing system (image 6): Production-relevant manufacturing of nanostructured surfaces on glass and polymer surfaces.

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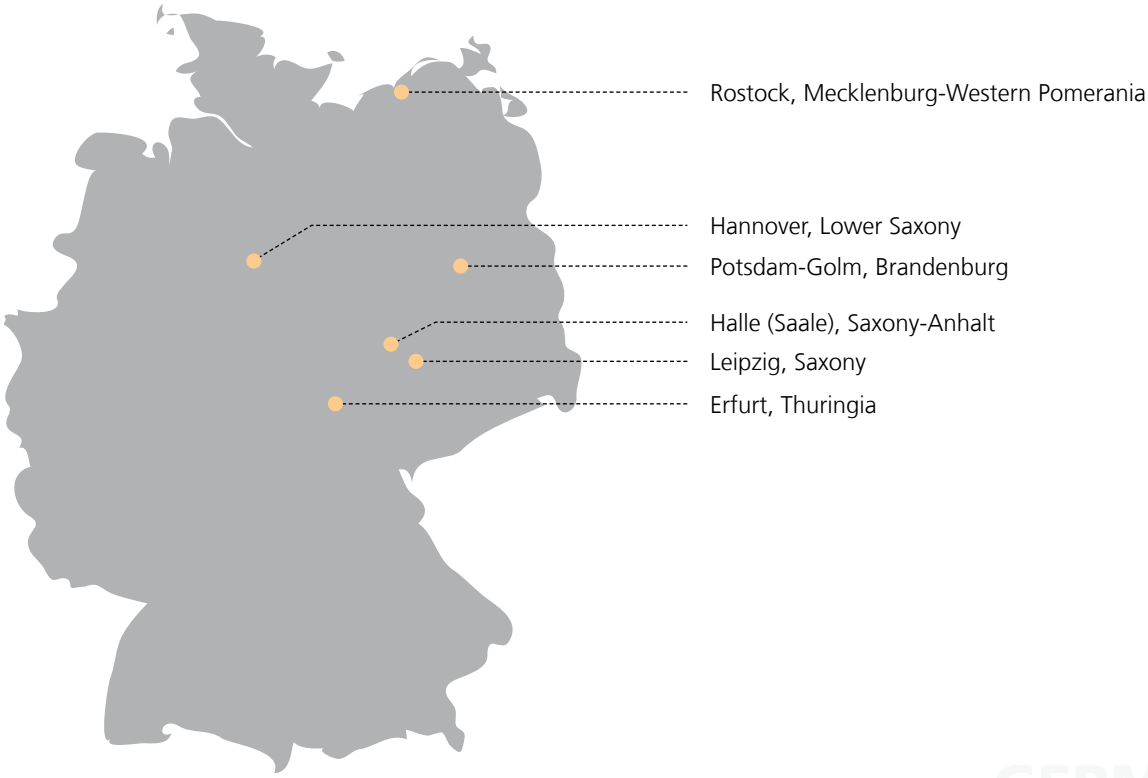
LOCATIONS



GERMANY

WORLDWIDE

LEIPZIG HEADQUARTERS, SAXONY, GERMANY

Perlickstraße 1, 04103 Leipzig, Germany
Usable area: 8 749 m²
Employees: 428
Focal areas: Cell engineering, cell therapy, drugs, diagnostics, immunology

Completed in April 2008, the main building boasts extensive laboratory capacities for conducting molecular and cell-biological work. An extensive immunohistochemistry laboratory, an isotope laboratory, a quality control laboratory with qualified equipment, as well as cyro-storage capacities also make up the institute's facilities.

The research infrastructure at the headquarters is complemented by various special facilities found in the extension buildings, which were opened in 2013 and 2015 (e.g. imaging units, laboratories for experimental medicine, a S3 laboratory, and clean-room facilities).

All of the Fraunhofer IZI's laboratories are certified according to S2 standards and therefore suitable for carrying out work in the fields of genetic engineering and infection biology. A flexible cluster structure allows laboratory sections to be adapted and fitted out in line with the specific requirements of a broad range of projects.

The business units Cell and Gene Therapy, Drugs and Diagnostics are primarily based in Leipzig. Biopharmaceutical products for clinical trials are manufactured in line with Good Manufacturing Practice (GMP) in the institute's clean-room facilities, which cover a total area of 1 000 m².

Management

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BIOANALYTICS AND BIOPROCESSING BRANCH OF INSTITUTE IN POTSDAM-GOLM, BRANDENBURG, GERMANY

Am Mühlenberg 13, 14476 Potsdam-Golm, Germany
Usable area: 4 096 m²
Employees: 121
Focal areas: Biotechnology, bioproduction, bioanalytics, automation

The Bioanalytics and Bioprocesses Branch in Potsdam-Golm was affiliated with the Fraunhofer Institute for Cell Therapy and Immunology on July 1, 2014. The site was initially founded in 2005 as a branch of the Fraunhofer IBMT and has since worked on technological solutions for biomedicine and diagnostics as well as for biotechnology and bioproduction.

The interdisciplinary team comprising natural scientists, engineers and technicians develops powerful, analytical methods for the detection and validation of pathogens and biological markers besides processes to obtain, handle and manipulate cells and biomolecules. In this context, the team develops applications for personalized medicine, as well as biosensors and detection procedures for the areas of agriculture and the environment, for a broad spectrum of substance classes.

The site has the state-of-the-art infrastructure required for miniaturizing and automating biological processes. This includes various biosensor and biochip technologies, pipetting robots and micro and nano-dispensers, besides many different rapid-prototyping procedures.

A further special feature of the branch's facilities is the life culture collection of cryophilic algae (CCCryo), which serves as a resource for developing production processes for novel, industrial bioproducts.

Management

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DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION IN HALLE (SAALE), SAXONY-ANHALT, GERMANY

Weinbergweg 22, 06120 Halle (Saale), Germany
Usable area: 1 300 m²
Employees: 62
Focal areas: Biochemistry, pharmacology, drug development, analytics

The Department of Drug Design and Target Validation develops new molecular therapies for neurodegenerative and inflammatory diseases. The department's expertise is based on an in depth pharma-like understanding of scientific work and a long-lasting experience in the field of drug development.

This profile encompasses the identification of new target proteins by analyzing putative pathologic post-translational modifications, the misfolding of proteins and the formation of pathological aggregates. Based on these new strategies the department develops and tests small molecules as well as biological agents (biologicals). This research is complemented by the design of new assays for the identification and diagnostic application of biomarkers aiming at monitoring the course of the disease and its therapy.

The department's expertise also expands to the generation of pharmacologically relevant in vitro and in vivo models. Besides state-of-the-art methods for peptide synthesis and protein analytics (MALDI-TOF and LC-MS), the department commands a wide range of biophysical methods to characterize therapeutically relevant physiological pathways, their key proteins as well as cell-based and pharmacologic models for the characterization of new chemical and biological drug candidates.

Management

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DEPARTMENT OF EXTRACORPOREAL IMMUNOMODULATION IN ROSTOCK, MECKLENBURG-WESTERN POMERANIA, GERMANY

Schillingallee 68, 18057 Rostock
Usable area: 700 m²
Employees: 27
Focal areas: Organ-supporting technologies, clinical trials

The department focuses on the development and evaluation of extracorporeal (outside the body) organ-supporting technologies with a particular emphasis on supporting the immune system.

The group offers the full range of preclinical and clinical analyses of extracorporeal technologies on the basis of a broad spectrum of in vitro simulations, small and large animal models as well as a powerful clinical study network for in- and outpatients. Moreover, the group offers self-developed unique analytic and diagnostic devices including an ex situ intestine model, a cell sensor and novel protein assays.

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BRANCH LAB TRANSLATIONAL CELL THERAPY IN HANNOVER, LOWER SAXONY, GERMANY

The Branch Lab Translational Cell Therapy develops and validates cell-based advanced therapy medicinal products (ATMPs). To do this, it conducts translational research and develops GMP-compliant manufacturing protocols for cell therapeutics at the interface to preclinical development right through to their transfer into clinical trials. Cell and genetic engineering methods and strategies are implemented and optimized here to specifically manufacture killer lymphocytes and their subpopulations. The ability to overcome so-called tumor immune escape mechanisms in cancer cells is key here. This is achieved by using activated and genetically modified effector cells together with checkpoint inhibitors and stimulating immune cells. These cell therapies boost immune surveillance and strengthen the elimination of resistant cancer cells as well as their malignant precursor cells (so-called tumor stem cells). Another focus of development lies in optimizing the transduction capacity of effector cells using chimeric antigen receptors (CARs) in order to increase cytotoxicity to malignant cells. To do this, human effector cells are separated following lymphapheresis by means of GMP-suitable, fully automated, closed-system production, genetically modified as necessary and expanded as part of clinical upscaling. Moreover, the group is developing GMP-compliant manufacturing and expansion protocols in order to proliferate a sufficient number of activated effector cells.

Management

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PROJECT CENTER MICROELECTRONIC AND OPTICAL SYSTEMS FOR BIOMEDICINE IN ERFURT, THURINGIA, GERMANY

The Microelectronic and Optical Systems for Biomedicine project center in Erfurt brings together the core competencies of three Fraunhofer institutes to span the disciplines of biosciences, microelectronics, microsystems technology, optics and photonics. This combined expertise will be used to develop application-ready systems in the areas of medical engineering, analytics, diagnostics, biotechnology, biophotonics, pharma, health care, ageing and food economics which will then be transferred into industry. Fields of application here include improved medical imaging and visualization as well as technologies for biomarker analysis.

Involved Fraunhofer Institutes

- Fraunhofer Institute for Applied Optics and Precision Engineering IOF (www.iof.fraunhofer.de/en)
- Fraunhofer Institute for Photonic Microsystems IPMS (www.ipms.fraunhofer.de/en)
- Fraunhofer Institute for Cell Therapy and Immunology IZI (www.izi.fraunhofer.de/en)

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FRAUNHOFER PROJECT CENTER FOR BIO-MEDICAL ENGINEERING AND ADVANCED MANUFACTURING (BEAM) AT MCMASTER UNIVERSITY, HAMILTON, ONTARIO, CANADA

The founding team at Fraunhofer IZI started looking for suitable Canadian cooperation partners back in 2011, a search that led to initial joint research projects being set up with McMaster University in Hamilton (Ontario, Canada). With approximately 29 000 students, the university is one of the most renowned in Canada, with particular strengths in the fields of health sciences, engineering and natural sciences. Over the past four years, McMaster University has attracted the most industry projects of all the universities in Canada.

In 2014, based on the huge success of ongoing cooperation projects, Fraunhofer-Gesellschaft decided to set up a Fraunhofer Project Center (FPC) at McMaster University. Governed by a cooperation agreement, the FPC is jointly run by experienced McMaster and Fraunhofer managers and is devoted to applied research in the business units Diagnostics, Automation, Cell Therapeutics and Biomaterials. Materials researcher Professor John Brennan and expert for bioengineering and drug delivery systems Professor Heather Sheardown are the center's key partners in terms of scientific cooperation and management on the Canadian side of the cooperation. The FPC also helps to establish German and Canadian companies and supports the development of business activities in the respective partner country.

Within the first few months of being established, the project center was already managing to attract significant funding on both the German and Canadian sides, besides a series of industry cooperation projects including approx. 12 million Canadian dollars in FedDev funding awarded in December 2015 for the construction of a joint research building in McMaster Innovation Park, which was opened in spring 2018. The new research building offers a state-of-the-art research infrastructure covering an area of approx. 1 900 m².

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JLCI – JOINT LABORATORY OF CHONNAM NATIONAL UNIVERSITY HOSPITAL HWASUN IN COLLABORATION WITH FRAUNHOFER IZI IN GWANGJU, JEOLLANAM-DO, SOUTH KOREA

Since 2010, Fraunhofer IZI has maintained a close cooperation with Chonnam National University Hospital Hwasun (CNUHH) in several areas. With 700 beds, the CNUHH is one of the largest university hospitals specialized in the treatment of cancer in South Korea. A vibrant biotech and medtech industry has established itself in the local area.

The JLCI facilitates the collaboration with external partners from academia and industry in Asia. For example the Fraunhofer IZI's ligand development group is using the regular access to fresh tumor materials from patients to identify tumor binding peptides, which already have been validated in tumor models.

The laboratory management is oriented at the standards and rules of the Fraunhofer-Gesellschaft. This shall guarantee a common basis when dealing with patents and contractual matters.

The JLCI was financed until 2017 by the Korean Ministry of Education, Science and Technology in Gwangju, Jeollanam-do, South Korea, as part of an initiative to strengthen international cooperation. Since 2018, additional funds have been authorized by the provincial government of Jeollanam do and the district of Hwasun gun in order to facilitate stronger connections within the industry and with other research institutes in Korea and Germany through professional business development.

Various projects have been conducted to date at the JLCI, e.g. in the field of senescence and cancer research, also as part of funding measures associated with the Federal Ministry of Economics and Technology's Central Innovation Program for SMEs. Several Fraunhofer IZI delegations have already taken part in conferences and research stays in Korea and a number of Korean colleagues have also worked at Fraunhofer IZI. The joint research work is documented in many joint publications. German-Korean symposia have so far taken place on an annually rotating basis.

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EVENTS

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2


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THE FRAUNHOFER IZI IN PUBLIC

Events are the key ingredient of the institute's communication strategy. The Fraunhofer IZI once again organized and supported various scientific and public events in 2018.

January 17, 2018: New Year's Reception 2018

March 7, 2018: BEAM research building opened

April 26, 2018: Girls'Day 2018 at the Fraunhofer IZI

May 5, 2018: Day of Science Potsdam

May 15, 2018: Workshop to improve the treatment of infectious cardiovascular diseases

June 22, 2018: Night of the Sciences in Leipzig: "Uncovering hidden worlds"

July 6, 2018: Night of the Sciences in Halle (Saale)

August 30, 2018: Fraunhofer IZI and Novartis announce continued cooperation at joint press conference

September 27, 2018: Fraunhofer Life Science Symposium in honor of Professor Frank Emmrich

October 4, 2018: Annual Conference BioTechnology 2020+

October 19, 2018: New Fraunhofer project center "Microelectronic and Optical Systems for Biomedicine" in Erfurt opens its doors

Looking to 2019

- January 24, 2019, New Year`s Reception
- March 28, 2019, Girls'Day 2019 and Boys'Day 2019, www.girls-day.de / www.boys-day.de
- April 9, 2019, Science cinema: Film and discussion on cancer medicine
- May 11, 2019, Potsdam Day of Science, www.potsdamertagderwissenschaften.de
- September 16–17, 2019, Fraunhofer Life Science Symposium & DG-GT Theme Day, www.fs-leipzig.com

Further information on the events can be found in the full version of the annual report on pages 116–121.
http://s.fhg.de/iiH

1 *Leipzig Fraunhofer institutes' joint New Year's reception.*
2 *Girls' Day 2018 at Fraunhofer IZI.*
3 *Insight into the future laboratory spaces of Fraunhofer's MEOS project center.*

FURTHERANCE

SPONSORS AND ADVISORY BOARD OF THE FRAUNHOFER IZI

The support and commitment of active institutions and individuals enable the Fraunhofer IZI to experience continuous and successful development as well as dynamic growth.

Sponsors

The Fraunhofer IZI would like to thank the European Union, the Federal Ministry of Education and Research, the Free State of Saxony and the City of Leipzig for their financial support.

The European Union sponsors through the programs EFRE and ESF. The building projects of the Fraunhofer IZI are sponsored 60 percent by the European Union and 20 percent each by the Federal Ministry of Education and Research and the Free State of Saxony. The plot of land is provided by the City of Leipzig in hereditary leasehold and free of charge. Furthermore, Fraunhofer IZI would like to thank the Leipzig Foundation for Innovation and Technology Transfer for its support during the institute's construction phase from 2005 to 2010.

European Union

Bundesministerium für Bildung und Forschung

Freistaat Sachsen

LEIPZIG

Advisory board

The advisory board functions as the external expert committee for strategic questions regarding the institutional direction and the Fraunhofer-Gesellschaft. Its members are invited and appointed by the president of the Fraunhofer-Gesellschaft. The advisory board includes representatives from industry and research as well as from authorities, ministries and foundations. The board meets once a year and evaluates the performance and image of the institute.

Members of the advisory board:

- Dr. Henrich Guntermann (Chair) (European Consortium of Technology Transfer S.A.)
- Uwe Albrecht (Mayor and Councillor for Economics and Labour, City of Leipzig)
- MR'in Dr. Annerose Beck (Saxon State Ministry of Science and the Arts (SMWK), Head of National-Regional Research Centers Administration)
- Bettina Berendsen (Sartorius Stedim Systems GmbH)
- Klaus Berka (Analytik Jena AG)
- Prof. Dr. Walter Brehm (Veterinary Medicine Faculty, Leipzig University, Dean)
- Prof. Dr. Jörg Gabert (Genolytic GmbH)
- Prof. Dr. Andreas H. Guse (University Hospital Hamburg-Eppendorf, Vice-Dean for Teaching)
- Prof. Dr. Hans-Martin Jäck (University Hospital Erlangen, Head of the Molecular Immunology Department, President of the German Society for Immunology)
- Prof. Dr. Markus Löffler (Leipzig University, Head of the Institute for Medical Informatics, Statistics and Epidemiology)
- Dr. Uwe Marx (Technische Universität Berlin / TissUse GmbH)
- Dr. Kai Pinkernell (Medigene AG)
- Dr. Mark Wolters (Bayer Pharma AG)

FRAUNHOFER-GESELLSCHAFT

THE FRAUNHOFER-GESELLSCHAFT IN PROFILE

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector and public administration.

At present, the Fraunhofer-Gesellschaft maintains 72 institutes and research units. The majority of the more than 26 600 staff are qualified scientists and engineers, who work with an annual research budget of more than 2.5 billion euros. Of this sum, more than 2.1 billion euros is generated through contract research. Around 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Around 30 percent is contributed by the German federal and state governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

International collaborations with excellent research partners and innovative companies around the world ensure direct access to regions of the greatest importance to present and future scientific progress and economic development.

With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer Institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, strengthening the technological base, improving the acceptance of new technologies, and helping to train the urgently needed future generation of scientists and engineers.

As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, at universities, in industry and in society. Students who choose to work on projects at the Fraunhofer Institutes have excellent prospects of starting and developing a career in industry by virtue of the practical training and experience they have acquired.

The Fraunhofer-Gesellschaft is a recognized non-profit organization that takes its name from Joseph von Fraunhofer (1787–1826), the illustrious Munich researcher, inventor and entrepreneur.

Executive board

Prof. Dr.-Ing. Reimund Neugebauer, President, Corporate Policy and Research Management, Technology Marketing and Business Models | Prof. Dr. Alexander Kurz, Human Resources, Legal Affairs and IP Management | Dipl.-Kfm. Andreas Meuer, Controlling and Digital Business Processes

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